Adverse Event Tracking as mandated by the Best Pharmaceuticals for Children Act

Pediatric Advisory Committee Meeting
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Best Pharmaceuticals for Children Act (1/4/02)

- Section 17: Adverse Event (AE) Reporting
  - Review AE reports during the one-year after pediatric exclusivity is granted
  - Report to the Pediatric Advisory Sub-Committee for review and recommendations (changed to Pediatric Advisory Committee by the Pediatric Equity Act, 2003)

AE Review Process

- Collaboration between
  - Office of Drug Safety (ODS)
  - Division of Pediatric Drug Development, OCTAP
  - Office of Pediatric Therapeutics (OPT)

AE Review Process (cont.)

- ODS Responsibilities
  - Review adverse events reported during the year after the date of exclusivity determination
  - Immediately discuss any serious unexpected events including deaths with OPT and OCTAP
  - Submit a written safety review within 90 days of the one-year post exclusivity date to OCTAP, OPT and Office of New Drugs

AE Review Process (cont.)

- OCTAP and OPT Responsibilities
  - Notifies Office of Drug Safety (ODS) of drugs granted/or denied exclusivity
  - Review ODS reports, individual AE reports and summaries of the pediatric clinical studies done for exclusivity
  - Develops presentations to the Pediatric Advisory Committee (AC) in consultation with ODS and OND
  - Focus the AC discussion on any serious AEs/Issues (e.g. SSRI and suicidality)

Adverse Event Report Review Template

- Executive Summary
- AERS search result:
  - Counts of AE reports including any deaths from drug *approval date* to *one-year post exclusivity determination date*
    - Adults (>16 year old) and Pediatric Ages (0-16 year old)
    - Domestic and foreign reports
    - Most frequently reported pediatric and adult adverse events

Adverse Event Report Review Template (cont.)

- Detailed Review of Pediatric AEs for the *One-Year Period Following the Granting of Pediatric Exclusivity*
  - Counts and labeling status of top 20 most frequently reported adverse event terms
  - Demographics, serious outcomes, indications and doses
  - Unexpected or unique pediatric adverse events
  - Increased frequency of known pediatric adverse events
  - Pediatric death reports
  - Summary adverse event profile

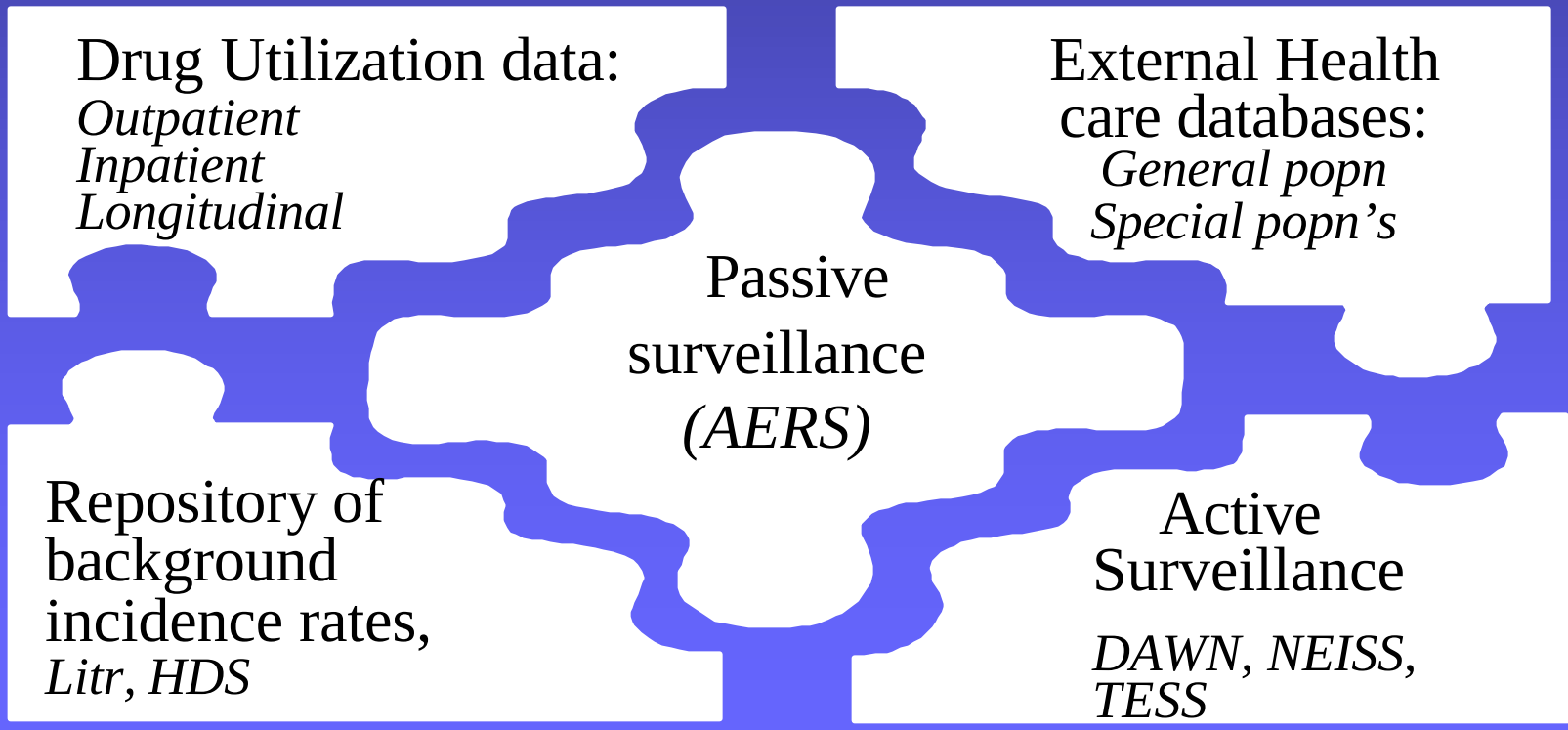
Drug Utilization Review Template

- Executive Summary
- Drug utilization data for adults and pediatric patients for 2 years prior and 1 year post exclusivity
  - Outpatient use
  - Inpatient use

Role of the Pediatric Advisory Committee

- Assess and discuss the presented adverse events
- If appropriate, recommend additional pediatric review and/or regulatory action
- Role is evolving

Components of the U.S. Comprehensive Postmarketing Drug Surveillance Program



Overview of FDA's Adverse Event Reporting System (AERS)

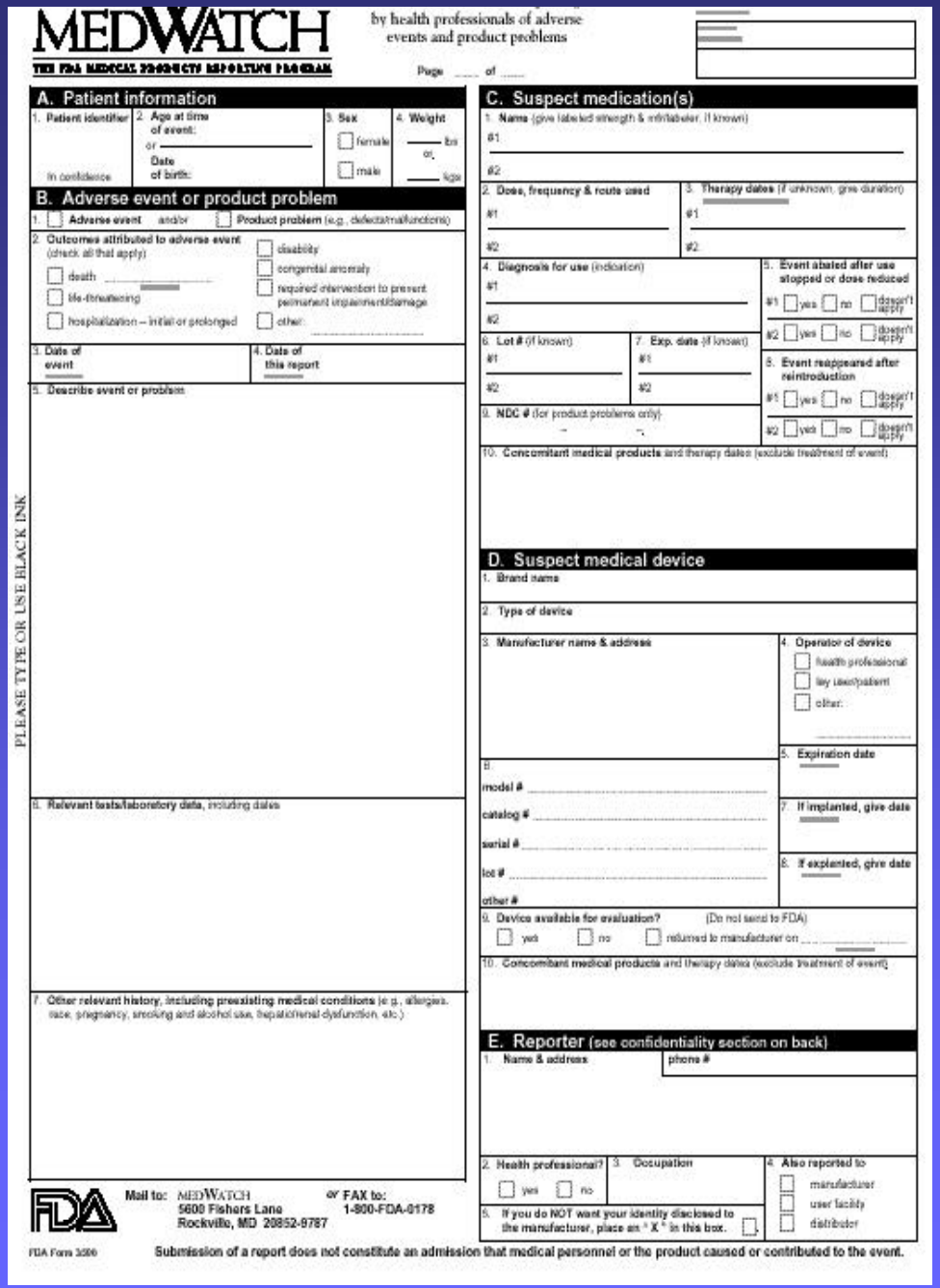
FDA Adverse Event Reporting System (AERS)

- Origin 1969 (Safety Reporting System until 1997)
- ~ 2 million reports in database
- Contains drug and "therapeutic" biologic adverse event reports
- Exception = vaccines
  VAERS 1-800-822-7967

Source of Reports

- Voluntary/spontaneous reporting
- Health care professionals, consumers/ patients, or others
- Manufacturers: Required for postmarketing reporting (>90%)
  - All adverse drug experience information obtained or otherwise received from any source, foreign or domestic

one form for all voluntary reporting [1993-present]



MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

by health professionals of adverse events and product problems

Page ____ of ____

A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — female / male
4. Weight — lbs or kgs

B. Adverse event or product problem

1. Adverse event and/or Product problem (e.g., defect/malfunction)
2. Outcomes attributed to adverse event (check all that apply): death; life-threatening; hospitalization – initial or prolonged; disability; congenital anomaly; required intervention to prevent permanent impairment/damage; other:
3. Date of event
4. Date of this report
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & manufacturer, if known) #1 #2
2. Dose, frequency & route used #1 #2
3. Therapy dates (if unknown, give duration) #1 #2
4. Diagnosis for use (indication) #1 #2
5. Event abated after use stopped or dose reduced #1 yes no doesn't apply; #2 yes no doesn't apply
6. Lot # (if known) #1 #2
7. Exp. date (if known) #1 #2
8. Event reappeared after reintroduction #1 yes no doesn't apply; #2 yes no doesn't apply
9. NDC # (for product problems only)
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device: health professional; lay user/patient; other:
5. Expiration date
6. model # catalog # serial # lot # other #
7. If implanted, give date
8. If explanted, give date
9. Device available for evaluation? (Do not send to FDA): yes no returned to manufacturer on
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address
phone #
2. Health professional? yes no
3. Occupation
4. Also reported to: manufacturer; user facility; distributor
5. If you do NOT want your identity disclosed to the manufacturer, place an "X" in this box.

PLEASE TYPE OR USE BLACK INK

FDA

Mail to: MEDWATCH, 5600 Fishers Lane, Rockville, MD 20852-9787 or FAX to: 1-800-FDA-0178

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

What to report?

Adverse events
product problems
medical errors associated with:

- ***Drugs [Rx and OTC]***
- ***Biological products***
- ***Medical devices***
- ***Dietary supp/herbal***

What Manufacturers Must Report (21CFR 314.80)

- Commercial marketing experience
- Postmarketing studies
- Scientific literature

  - All domestic spontaneous reports
  - Foreign and literature reports - Serious, Unlabeled
  - Study reports - Serious, Unlabeled, "Reasonable Possibility" that event is related to drug

FDA Postmarketing Definitions (21 CFR 314.80)

- Adverse Drug Experience: any adverse event associated with the use of a drug, whether or not considered drug related, including
  - Accidental or intentional overdose
  - Occurring from abuse or drug withdrawal
  - Failure of expected pharmacological action

FDA Postmarketing Definitions (21 CFR 314.80)

- Serious ADE: any event occurring at any dose that results in any of the following outcomes:
  - Death
  - Life-threatening ADE (immediate risk)
  - Hospitalization or prolongation of hospitalization
  - Persistent/significant disability/incapacity
  - Congenital anomaly/birth defect
  - Other/requiring intervention (eg. bronchospasm)

FDA Postmarketing Definitions (21 CFR 314.80)

- Unexpected ADE: any event not listed in the current labeling for the drug product including events that may be symptomatically and pathophysiologically related to a labeled event, but differ because of greater severity or specificity (e.g. hepatic necrosis vs hepatitis)

Strengths of AERS

- Includes all U.S. marketed drug products
- Simple, less expensive reporting system than active system
- Provides for early detection of safety signals
- Especially good for rare adverse drug events (anaphylaxis, liver failure, aplastic anemia, serious skin reactions)

Limitations of AERS

- Underreporting: varies from drug to drug and over time
- Quality and completeness of reports: variable, often poor
- Cannot estimate true adverse event risk rate
  - Numerator uncertain
  - Denominator must be estimated, virtually impossible for inpatient & OTC drugs

Pediatric Drug Utilization Data

Outpatient Drug Use: Data Sources and Limitations

- IMS Health, National Prescription Audit *Plus*? provides an estimate of the total number of prescriptions dispensed from retail pharmacies in the U.S., but does not provide demographic information on prescription use.

- IMS Health, National Disease and Therapeutic Index? is a survey based on a sample size of 2000 - 3000 office-based physicians. The small sample size can make these data projections unstable, particularly when use is not prevalent as in the case of the pediatric population.

Outpatient Drug Use: Data Sources and Limitations

- IMS Health, National Sales Perspectives™ Retail and Non-Retail does not provide a direct estimate of use but does provide a national estimate of units sold from the manufacturer to various channels of distribution. It does not include demographic information for the patients receiving these products, such as age and gender. The amount of products purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use.

Inpatient Drug Use: Data Sources and Limitations

- AdvancePCS? , a wholly-owned subsidiary of Caremark Rx, Inc., is based on a large prescription claims database among an insured population of over 75 million patient lives, but data cannot be projected nationally

- Premier, Inc. contains inpatient drug use from 450 acute, short-stay, non-federal hospitals. National projection methodology is available but the ability to make accurate national estimates is selective; drug use cannot be linked to diagnosis or procedure; treatments administered at hospital outpatient clinics not included.

Inpatient Drug Use: Data Sources and Limitations

- Child Health Corporation of America™ (CHCA) Pediatric Health Information System (PHIS)
  - Inpatient data from 29 free-standing children's hospitals with charge level drug utilization data
  - Not possible to directly link drug use with specific diagnoses or procedures; therefore, associations should be made with caution
  - Data cannot be projected nationally

Drug Adverse Events Presented at Peds Adv. Committee Meetings

- June 2003
  - Sertraline
  - Oxybutynin
  - Atorvastatin
  - Simvastatin
- Oct 2003
  - Busulfan
  - Cetirizine
  - Losartan
  - Tamoxifen
  - Quinapril
  - Nefazodone
- Feb 2004
  - Paroxetine
  - Pravastatin
  - Citalopram
  - Vinorelbine
- June 2004
  - Topotecan
  - Temozolomide
  - Venlafaxine
  - Moxifloxacin ophthalmic
  - Cipropfloxacin ophthalmic
  - Fosinopril
  - Fexofenadine
  - Fentanyl transdermal

Examples of Outcomes of Prior Pediatric Advisory Sub-Committee Meetings

- SSRI/SNRIs
  - Class labeling for suicidal behavior
  - Class labeling for neonatal withdrawal
- Fentanyl Transdermal
  - Strengthen black box warning by adding "inappropriate use resulting in deaths"
  - Highlight prescriber qualifications
  - Simplify language in patient information

Today's Agenda for BPCA Mandated AE Review

- Ofloxacin and alendronate
  - Hari Sachs, MD
- Fludarabine
  - Susan McCune, MD, MA Ed
- Desloratadine
  - Jane Filie, MD

Agenda (cont.)

- Perspective on safety for orally inhaled and intranasal Budesonide and Fluticasone
  - Peter Starke, MD
- Studies performed for pediatric Written Request
  - ShaAvhrée Buckman, MD, PhD
- Adverse Events reported in the one-year post-exclusivity period
  - Joyce Weaver, PharmD
- Summary comments
  - Badrul A. Chowdhury, MD, PhD

Question for the Committee

- Based on the presentations you have heard today regarding drugs containing fluticasone or budesonide, do you have any concerns about the use of these drug products as labeled?